

Department Chemistry
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Computation Notebook

11 3/4" x 9 1/4", 4 x 4 Quad., 75 Sheets

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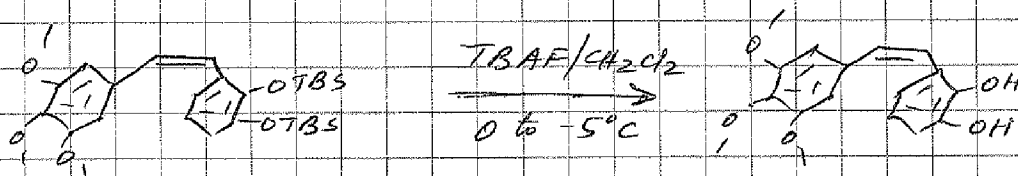
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DEPROTECTION USING TBAF

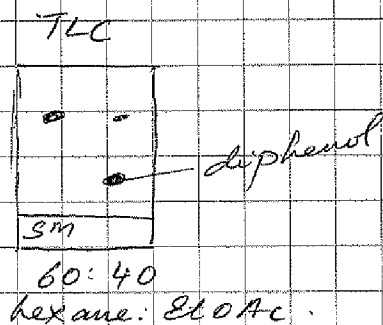
07/04/02



MF	SM	TBAF in 1M THF	CH_2Cl_2 dry Solvent.
MW	530.84	261.47	
Ratio	1	2.5	
Wt(g)	2.02	2.49 (9.53ml)	
mmoles	3.81	9.53	

PROCEDURE:

1. Dried the compound on pump for 12 hour.
2. Put under Ar.
3. Dissolve in CH_2Cl_2
4. Maintain temperature at -5°C by using ice bath to which NaCl is added.
5. TLC was done after 15 min, 20, 25, 30, 35 min
6. Reaction was stopped after 35 min by quenching with H_2O .



7. Transferred to a separatory funnel and some more H_2O and do partitioning.

8. Collect the lower organic layer
9. Extract the aqueous layer with CH_2Cl_2 twice.
10. The combined organic layers were dried with anhydrous Na_2SO_4 .
11. Filtered & rotavaped.

COLUMN CHROMATOGRAPHY.

07/05/02

Did a column to collect purified diol.

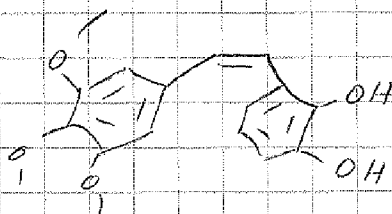
Used 70:30 hexane: EtOAc.

Wt of diol collected = 0.5 g.

NMR.

^1H NMR PA-11-56

^{13}C NMR PA-11-57

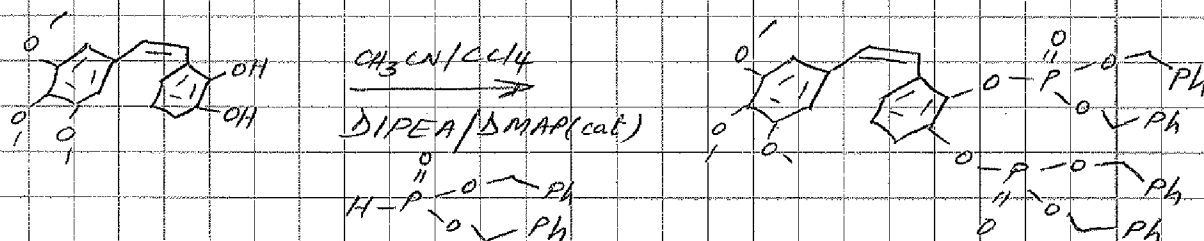


$$\text{Yield \%} = \frac{0.5}{302.32} = 1.66 \text{ mmol}$$

$$\frac{1.66}{3.81} \times 100 = 43.40\%$$

DIBENZYLPHOSPHORYLATION OF $\Delta 104$

07/06/02



MF	SM	CCl_4	DIPEA	DMAP	DBP	KH_2PO_4 (0.5M)	CH_3CN
MW	302	153.82	129.24	122.17	262.25	136.09	
wt(g)	0.5(g)	2.53(1.6ml)	0.89(1.2ml)	0.04	1.26(1.06)		10ml
Ratio	1eq	10eq	4.2eq	0.2eq	2.9eq		
mmoles	1.65	16.5	6.95	0.33	4.8		

PROCEDURE Ref Petit Antineoplastic agents 429 pg 207

1. The diphenol was put Ar, cool to -20°C
2. Add CH_3CN , then add CCl_4 and stir for 10 min
3. Diisopropyl ethyl amine and DMAP were then added.
4. 1 minute later dibenzyl phosphite was added and temperature was maintained below -20°C
5. After 45 min do TLC to check compound formation

TLC



60:40
hexane: EtOAc

DBP (almost same R_f as SM)

6. Then KH_2PO_4 (0.5M) was added and the

7. It was extracted with EtOAc, 4 times then washed with saturated NaCl and water and dried with anhydrous NaCl
8. It was rotavaped and the yellowish brown mixture was separated by column chromatography.

COLUMN CHROMATOGRAPHY

Separated by flash chromatography using 70:30 hexane: EtOAc

then use 60:40 hexane: EtOAc

Colourless oily liquid wt = 0.71 g.

¹H NMR PA-11-58

³¹P NMR PA-11-59

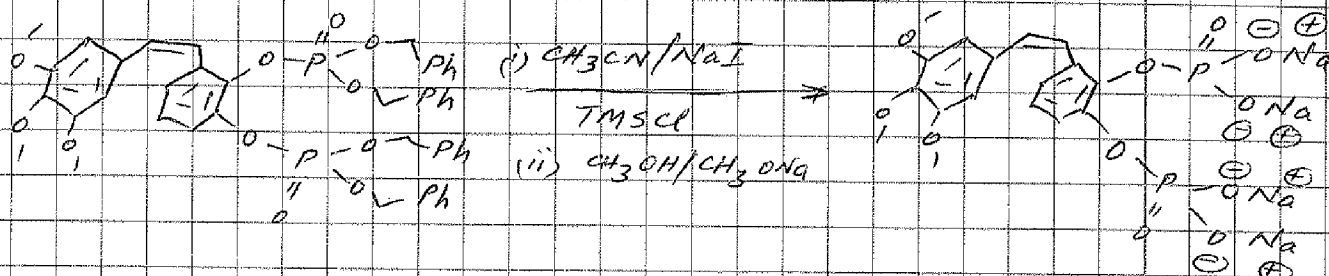
¹³C NMR PA-11-60

$$\text{yield} = \frac{0.71}{822.77} = 0.86 \text{ mmol}$$

$$\% = \frac{0.86}{1.65} \times 100 = 52.29\%$$

TETRASODIUM - DIPHOSPHATE

07/09/02

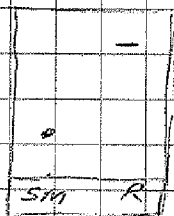


MF	SM	NaI	TMSCl	$\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$	CH_3ONa 25%	CH_3CN	CH_3OH
	822						
MW	822	149.89	108.64	248	54.02	9.5ml	
Wt(g)	0.71	0.52	0.37 (0.45ml)	1ml	0.19 (0.8ml)		
mmoles	0.86	3.44	3.44		3.44		
Ratio	1 eq	4 eq	4 eq	1%	4 eq		

PROCEDURE: Ref Petit Antineoplastic agents 429 pg 207.

1. The phosphate was put under Ar.
2. CH_3CN was added to it, followed by NaI .
3. The mixture was stirred for 2 mins, then chlorotrimethylsilane (distilled using CaH_2) was added dropwise.
4. 30 min later TLC was done to ensure that the SM was used up.

TLC



60:40 hexane: EtOAc.

5. Reaction was terminated by adding 1% $\text{Na}_2\text{S}_2\text{O}_3$.

7. The mixture was dissolved in $H_2O - CH_2Cl_2$
8. The CH_2Cl_2 layer was washed with H_2O three times.
9. The aqueous layer was concentrated using toluene azeotrope
10. The crude was dried on vacuum pump overnight
11. The dry mixture (looked like foam and was dark brownish in colour) was dissolved in CH_3OH , then CH_3ONa was added and the solution was stirred for 6 hours

RECRYSTALLISATION

07/12/02

Tried recrystallizing using $H_2O - Ethanol$.
 $H_2O - methanol$
 $H_2O - acetone$

did not work.

Separated 40mg using prep TLC (70:30 water isopropanol)

Got 10mg of the trans isomer.

Separated 15 fractions by prep TLC

SEPARATION USING C-18 COLUMN

07/15/02

Tried separation using $CH_3OH : H_2O : CH_3CN$ system (approx 55:10:35)

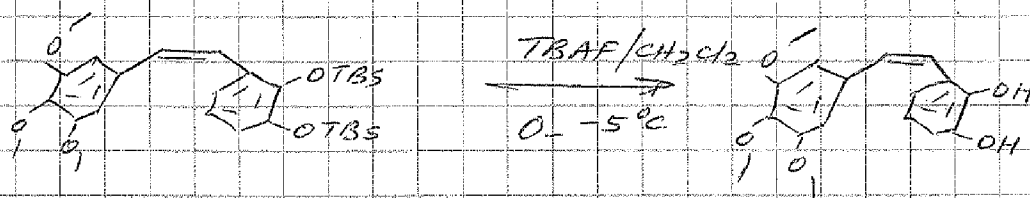
using C18 column first run methanol thro' it (least polar)

The compound came out as a mixture.

Tried separation on prep TLC. It was a disaster.

DEPROTECTION USING TBAF

07/30/01

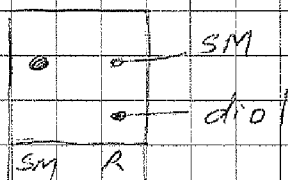


MF	SM	TBAF in 1M THF	CH_2Cl_2 (dry) solvent
MW	530.84	261.47	
Ratio	1 eq	2.5 eq	
Wt (g)	3.8375	4.73 (18.1 ml)	
mmoles	7.24	18.1	

PROCEDURE

1. The compound was put under Ar and dissolved in CH_2Cl_2 .
2. It was cooled to -5°C by adding common salt to ice bath.
3. TBAF was added and TLC done after 15 mins.

TLC



70:30 hexane:EtOAc.

4. Reaction was continued for 50 min till all the SM was used up.



70:30 hexane: EtOAc.

5. The reaction was quenched with water & extracted the aqueous layer with CH_2Cl_2 thrice.
6. The combined organic layers were dried over Na_2SO_4 anhydrous, filtered and rotavaped.
7. The dark brown colour oily crude was purified by column chromatography.

COLUMN CHROMATOGRAPHY.

The compound was purified by flash column chromatography using hexane: EtOAc 60:40 to yield 2.05g of diol.

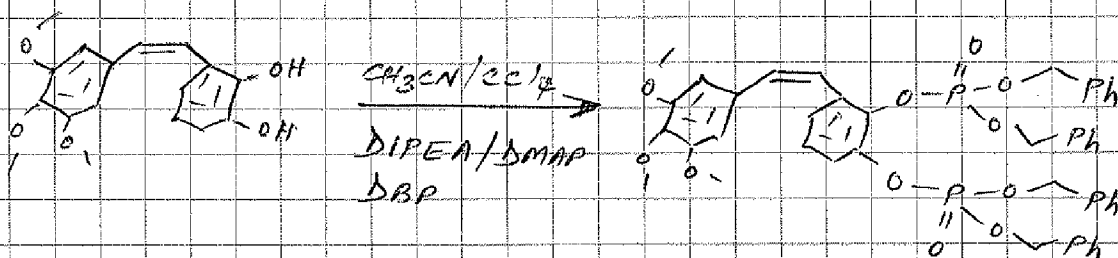
$^1\text{H-NMR}$ PA-11-81

$$\text{yield\%} = \frac{2.05}{302.32} = 6.78 \text{ mmols}$$

$$\frac{6.78}{7.24} \times 100 = 93.65\%$$

DIBENZYL PHOSPHORYLATION

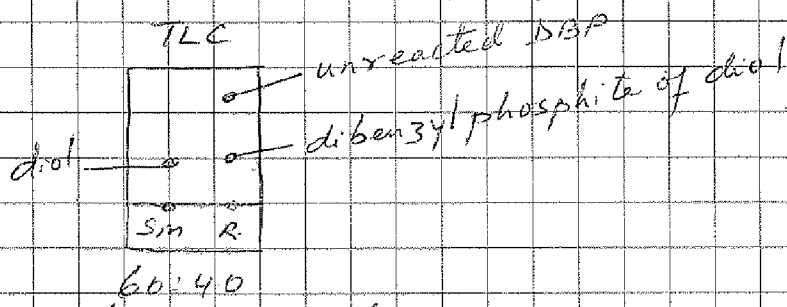
08/01/02



MF	SM	CCl ₄	DIPEA	DMAP	DBP	CH ₃ CN	KH ₂ PO ₄ 0.5M
MW	302.32 0.86	153.82	129.24	122.17	262.25		136.09
Wt(g)	0.86	4.46 (28ml)	1.57 (22ml)	0.07	2.2 (1.85ml)	17ml	
Ratio	1eq	10eq	4.2eq	0.2eq	2.9eq		
mmoles	2.85	28.5	12.2	0.57	8.3		

PROCEDURE: Ref G.R. Pelt, *Anti-Cancer Drug Design* (2000),
15, 203-216

1. The diphenol was put under Ar.
2. It was cooled to -20°C . Then CCl_4 was added and stirred for 10 min.
3. DIPEA and DMAP were then added.
4. After stirring for 1 min dibenzyl phosphite was added and temperature maintained below -20°C .
5. After 45 min, TLC was performed.



6. The dibenzylphosphorylated compound appears at almost the same R_f as diol (watch carefully).
7. The reaction was quenched with 0.5M KH_2PO_4 and the mixture was allowed to come to r.t.
8. The aqueous layer was extracted with EtOAc four times, washed with brine, then with H_2O and dried using Na_2SO_4 anhydrous.
9. It was filtered and rotaraped.

COLUMN CHROMATOGRAPHY.

08/02/02

The compound was loaded on column (wet loading) and flash column chromatography was performed using 3:2 hexane-ethyl acetate to afford ^{1.73}1.8g of a colourless oil.

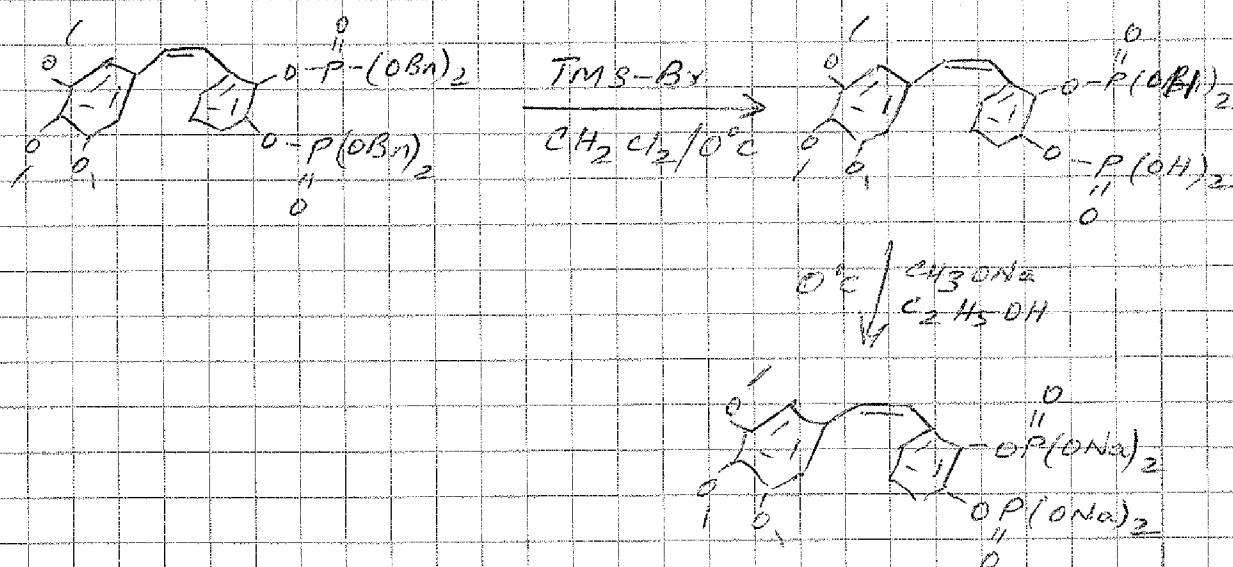
 ^1H NMR PA-11-82 ^{31}P -NMR PA-11-83

$$\text{yield\%} = \frac{1.73}{822.77} = 2.10 \text{ mmol}$$

$$\frac{2.10}{2.85} = 73.77\%$$

TETRASODIUM DIPHOSPHATE

08/03/02



PROCEDURE: Ref G. R. Petit et al. Anti Cancer Drug Design (2001) 16, 185-193.

MF	SM	TMSBr	CH_2Cl_2	$\text{C}_2\text{H}_5\text{OH}$	CH_3ONa
MW	822	153.10			54.02
Wt(g)	0.12	0.089 (0.08 ml)	1 ml	2.2 ml	0.032
mmoles	0.146	0.583			0.583
Ratio	1 eq	4 eq			4 eq
					$\text{Na}_2\text{S}_2\text{O}_3$ 10% (300) \rightarrow 1.1 ml

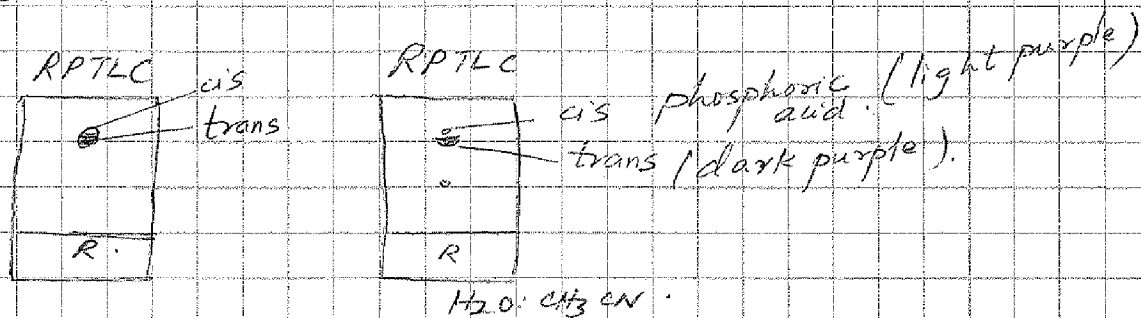
PROCEDURE:

1. The tetra benzyl ester was put under Ar
2. It was dissolved in DCM at 0°C & bromo trimethyl silane was added.
3. After stirring for 15 min, TLC was done.

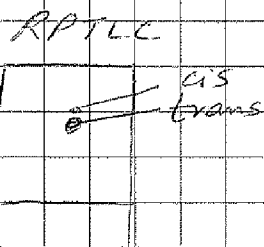
TLC

faint quickly disappear (di benzyl bromide)

4. The reaction was quenched with 10% $\text{Na}_2\text{S}_2\text{O}_3(\text{aq})$ after 2.5 min.



5. Isomerization had already taken place with a greater percentage going to trans and there was minor formation of cis.
6. The solvent aqueous layer was removed with a disposable pipette. It was extracted with EtOAc three. The combined organic layers were rotavaped and then dried on the vacuum pump. It took very long to dry even after 12 hours, it wasn't looking very dry.
7. It was then put under Ar, maintained at 0°C and dissolved in $\text{C}_2\text{H}_5\text{OH}$.
8. Sodium methoxide was quickly added and stirred for 30 min. Light yellow colour precipitate was obtained which was rotavaped.
9. It was triturated with ether, turned dark brown. TLC showed greater formation of trans.

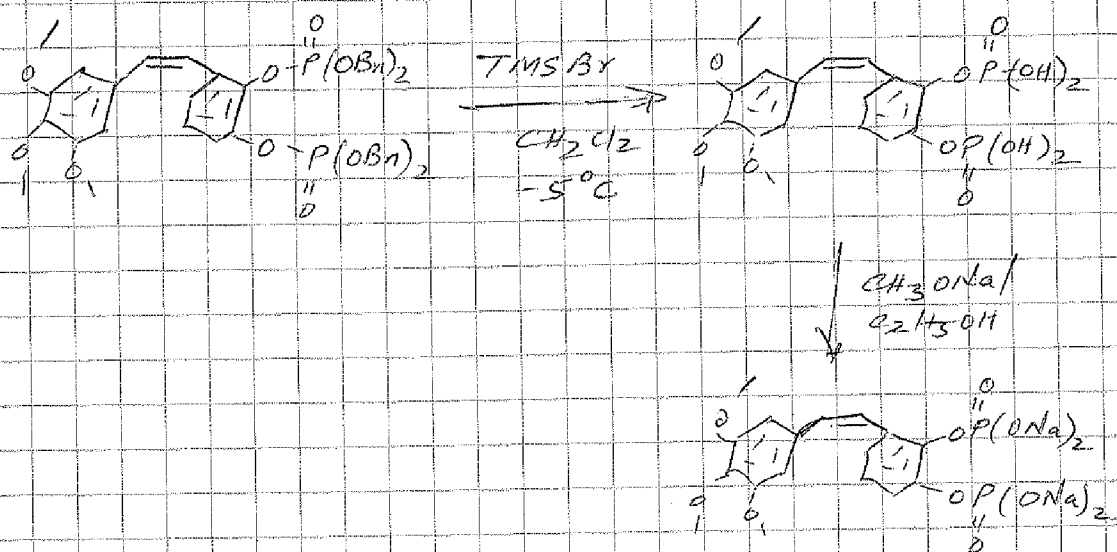


70:30 Water: Isopropanol

10. RECRYSTALLIZATION from water, acetone was attempted but failed.

TETRA SODIUM DIPHOSPHATE

08/05/02



PROCEDURE: Ref G. R. Pettit et al. *Anti Cancer Drug Design* (2001)
16 pg 185-193

SMF	SM	TMSBr	CH ₂ Cl ₂	CH ₃ ONa	C ₂ H ₅ OH	Na ₂ S ₂ O ₃ 1%
MW	822	153.10		54.02		
Wt (g)	0.100	0.075 (0.044 ml)	0.9 ml	0.026	1.8 ml	0.9 ml
mmoles	0.12	0.486		0.486		
Ratio	1 eq	4 eq		4 eq		

PROCEDURE: Ref G. R. Pettit et al. *Anti Cancer Drug Design* (2001)
16, 185-193

1. To a stirred solution of tetra-benzyl ester in CH₂Cl₂ under Ar at 0°C - (-5°C), bromotrimethylsilane was added.
2. After stirring for 5 mins, TLC was done.



faint and quickly disappeared
perhaps dibenzyl bromide
is highly volatile

60:40
hexane: EtOAc

RP TLC



H₂O: CH₃CN
70: 30

RP TLC

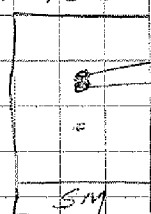


H₂O: Isopropanol
70: 30

phosphoric
acid inter-
mediate

3. However the reaction was quenched with 1% Na₂S₂O₃ in CH₃COOH (Note: no water was used) only after 15 min as the RP TLC plates took long to develop.
4. The solution was rotavaped using Toluene azeotrope & then CH₂Cl₂.
5. A TLC was performed after rotavaping off the solvent.

RP TLC

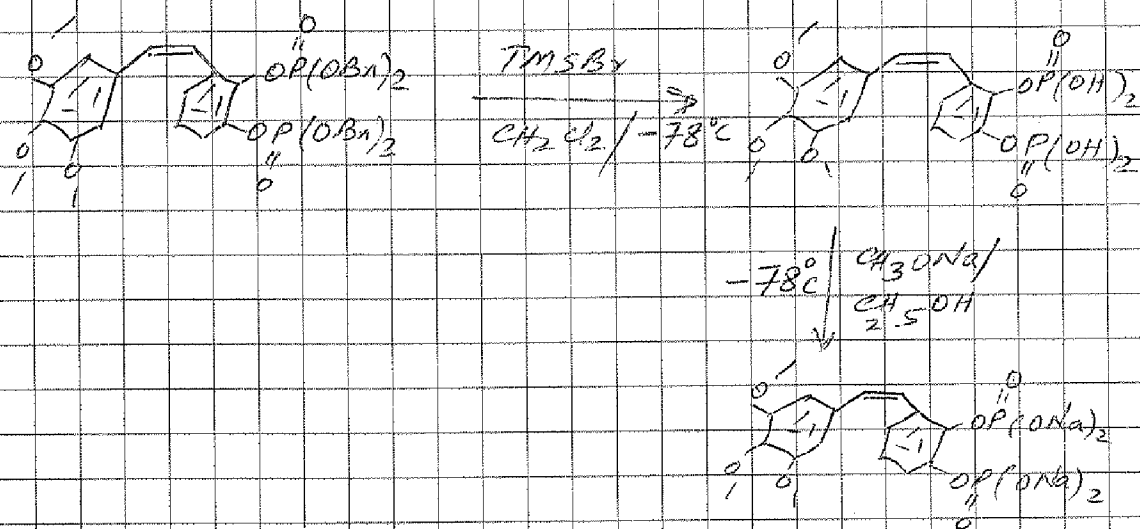


70:30 Water: Isopropanol

6. Perhaps the isomerization took place after 5 min.
7. The compound (crude) was dried light yellow mixed with brown (mustard colour) on the vacuum pump for 6 hours. It dried and was like a foam.
8. The dried crude was put under Ar, dissolved in C₂H₅OH at 0°C.
9. NaOCH₃ was quickly added and stirred for 30 mins. The compound was taken out, it was white in colour and rotavaped.
10. It was triturated with anhydrous diethyl ether.

TETRASODIUM DIPHOSPHATE

08/07/02



MF	SM	TMSBr	CH ₂ Cl ₂	CH ₃ ONa	C ₂ H ₅ OH	Na ₂ S ₂ O ₃ (10%)
MW	822	153.10		54.02		
Wt(g)	0.13	0.098	1.2 ml	0.035	2.4 ml	1.2 ml
mmoles	0.16	0.64		0.64		
Ratio	1 eq	4 eq		4 eq		

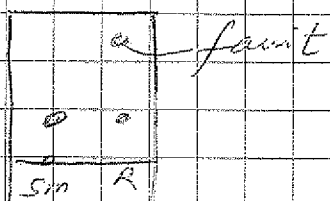
PROCEDURE: Ref. GR Petit et al, Antineoplastic agents 460
 Anti Cancer Drug Design (2001), 16, 185-193

1. The tetra-benzyl ester was put under Ar
2. Temp was -78°C. It was dissolved in Dichloro-methane.
3. TMSBr was added & temp maintained at -78°C
4. After stirring for 5 min, 15 min, 30 min, 45 min, TLC was done.

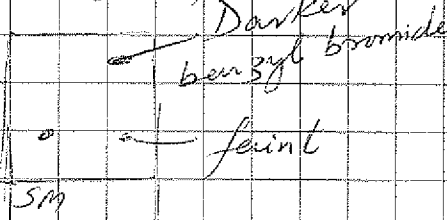
TLC (5 min)

very light

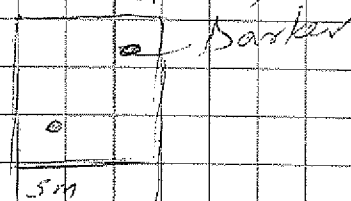
TLC (15 min)

60:40
hexane: EtOAc

TLC (30 min)

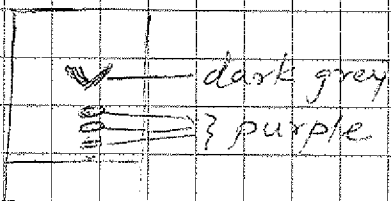
60:40
hexane: EtOAc

TLC (45 min)

60:40
hexane: EtOAc

5. After stirring for 45 min the rxn was quenched with 10% $\text{Na}_2\text{S}_2\text{O}_3$ (aq) and stirred for 5 more min. It looked like a creamy ppt mixed with an oily layer.
6. The creamy layer was removed using a disposable pipette into a t.t. It was extracted with EtOAc thrice.
7. The combined organic layers were rotavaped finally a little CaH_2 was added and rotavaped.
8. A colourless oily liquid (phosphoric acid) intermediate was obtained which was dried on the vacuum pump.

RP TLC

70:30
water: CH_3CN